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ORIGINAL

The assessment of total antioxidant capacity and superoxide dismutase levels, and the possible role of manganese superoxide dismutase polymorphism in acromegaly

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Abstract. Oxidative status is attributed to endothelial dysfunction and might be one of the key mechanisms of endothelial dysfunction in acromegaly. In this study, we aimed to investigate the effect of acromegaly on superoxide dismutase (SOD) and total antioxidant capacity (TAC) levels, and the possible influence of human manganese superoxide dismutase (MnSOD) polymorphism on these levels. 51 acromegaly patients and 57 age and sex matched healthy subjects were recruited to the study in Bezmialem Vakif University Hospital between 2011 and 2014. The median SOD and TAC levels were 42.7 (33–60) pg/mL and 1,313.7 (155–1,902) μM in acromegaly; and 46.3 (38–95) pg/mL and 1,607.3 (195–1,981) μM in healthy subjects ($p < 0.001$, $p < 0.001$). SOD levels were decreased in controlled and uncontrolled patients compared to healthy subjects ($p = 0.05$ and $p = 0.002$, respectively). Controlled and uncontrolled acromegaly displayed significantly decreased levels of TAC compared to healthy subjects ($p < 0.05$ and $p < 0.001$, respectively). SOD levels were not associated with MnSOD polymorphisms in acromegaly. In conclusion, this study showed that acromegaly was associated with decreased levels of SOD and TAC, and controlling the disease activity could not adequately improve these levels.

Key words: Oxidative status, Acromegaly, Total antioxidant capacity, Superoxide dismutase

ACROMEGALY is a rare disease characterized by growth hormone (GH) hypersecretion usually caused by a GH-secreting pituitary adenoma [1]. Along with increased risk for cardiovascular mortality and morbidity, endothelial dysfunction is a well-recognized condition in the course of acromegaly [2, 3]. Increased formation of reactive oxygen species (ROS) and/or reduced antioxidative capacity are attributed to endothelial dysfunction, and oxidative stress is a putative pathophysiological link between endothelial dysfunction and acromegaly [4, 5]. The clinical studies focused on investigation of oxidative stress in acromegaly are very limited. Acromegaly was attributed to oxidative stress through the mechanisms of decreased nitric oxide, catalase, oxidized glutathione and increased thiobarbituric acid reactive substance (TBARS) levels [6]. Also, high ceruloplasmin activity was associated with increased oxidized low-density lipoprotein in patients with active acromegaly [7]. However, the status of oxidative stress regarding the effect of disease activity is lacking.

Total antioxidant capacity (TAC) provides an estimation of antioxidant activity which includes those antioxidants not yet recognized or not easily measured and represents the overall free radical scavenging ability of

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various antioxidants [8]. TAC is a useful measurement for investigating oxidative stress and has been implicated in the pathological mechanisms of many diseases including atherosclerosis, diabetes, hypertension and some types of cancers [9-12].

Human manganese superoxide dismutase (MnSOD) is one of the major cellular defense enzymes that plays a primary role in the detoxification of ROS [13, 14]. Superoxide dismutase (SOD) is the only mitochondrial enzyme that catalyzes the dismutation of superoxide anion radical (O2−) into oxygen and hydrogen peroxide [15]. The human MnSOD gene is located on chromosome 6 which has a single nucleotide polymorphism (SNP) at codon 16 (rs4880) that encodes for either alanine (Ala) or valine (Val) at the –9 position in the mitochondrial targeting sequence. While the Ala MnSOD variant is related to high mitochondrial enzymatic activity, the Val MnSOD variant is associated with low enzymatic activity [14]. MnSOD polymorphisms have been associated with common diseases such as diabetes, coronary artery disease and metabolic syndrome [16-18].

In this study, we aimed to investigate the measurement of TAC and MnSOD levels and the influence of disease activity on these levels in acromegaly patients. The possible role of genetic phenotypes in MnSOD was also studied.

Material and Methods

Patients

Fifty-one acromegaly patients (33 females and 18 males) and 57 age and sex matched healthy subjects (44 females and 13 males) were recruited to the study between 2011 and 2014 in the Endocrinology Clinic of Bezmialem University Hospital, Turkey. The median age was 44 (22–83) years in the acromegaly group and 42 (18–74) years in healthy subjects. The cardiovascular risk factors for healthy subjects were registered, they had no endocrine disease and they were not receiving any treatment including antioxidants or any drug known to affect lipids or biomarkers of cardiovascular disease. The diagnosis of acromegaly was based on clinical features and was confirmed by GH unsuppression to <0.4 ng/mL after an oral glucose tolerance test and high IGF1 levels age matched [19]. Magnetic resonance imaging (MRI) of hypophysis was performed on all acromegaly patients and maximum diameter was determined as the tumor size. Acromegaly was considered to be in biochemical remission, if nadir GH < 0.4 ng/mL during an OGTT or under random GH < 1 ng/mL for patients receiving medical treatment and normal age matched IGF1 levels [4]. IGF1 values were adjusted as 100 × IGF1/Upper limit of normal range [IGF1 norm (%)]. We classified acromegaly patients as controlled and uncontrolled, to investigate the influence of disease activity on SOD and TAC levels. There were 24 patients in the controlled group and 27 patients in the uncontrolled group.

Blood GH and IGF1 levels were assayed using a chemiluminescence immunometric assay (Siemens Advia-Centaur USA). Age-related reference ranges for IGF1 were as follows: 18–20 y: 197–956; 20–23 y: 215–628; 23–25 y: 169–591; 25–30 y: 119–476; 30–40 y: 100–494; 40–50 y: 101–303; >50 y: 78–258 (ng\mL).

This study was approved by the local ethics committee of Bezmialem University and informed consent was obtained in all cases.

SOD Assay

Peripheral venous blood was collected in serum tubes (10 mL) and centrifuged at 1,500 rpm/min for 10 minutes to obtain the serum aliquots and stored at –80°C until further assay. SOD levels were determined with an enzyme-linked immunosorbent assay kit (BMassay, Beijing, China) according to the manufacturer's instructions. The plates were read in a spectrophotometer at a relative optical density of 450 nm within 30 min after adding the stop solution. The referenced normal range of SOD is 1.56–100 U/mL.

TAC Assay

TAC levels were measured by the modified CUPRAC method [20]. One milliliter of 1.0×10^{-2} M $CuCl_2.2H_2O$, 1 mL of 7.5×10^{-3} M Nc, and 2 mL of pH 7.0 urea buffer were mixed. To this mixture were added (1.0 – x) mL of pH 8.0 standard buffer and (x) mL serum sample or standard antioxidant solution. The final mixture at 5.0 mL total volume was let to stand at room temperature for exactly 30 min, and the absorbance at 450 nm was recorded against a reagent blank. (To minimize the serum sample consumption the volumes of all the reagents and samples can be reduced five times proportionally to get only 1.0 mL total volume.)

Genotyping of MnSOD

MnSOD polymorphism detection was carried out by restriction fragment length polymorphism (RFLP) method. Polymerase chain reaction (PCR) method was used for amplification of the MnSOD gene using forward

primer 5'-ACC AGC AGG CAG CTG GCG CCGG-3' and reverse primer 5'-GCG TTG ATG TGA GGT TCC AG-3'. A PCR reaction mix, which contains 150 ng DNA template, 15 mM $MgCl_2$, 50 mM KCl, 10 mM Tris-HCl and 200 μM each of deoxynucleotides and Taq DNA polymerase (MBI Fermantas, Vilnius, Lithuania) was used. The PCR reactions were thermally cycled with an initial denaturation step at 95°C for 5 min, followed by 35 cycles of 94°C for 45 s, 61°C for 45 s and 72°C for 45 s, and then a final extension step at 72°C for 5 min. The 107-base pair PCR product was digested by PdiI (MBI Fermantas) at 37°C for 16 hours and analyzed with agarose-gel electrophoresis. The Val/Val genotype shows only one band of 107 bp in agarose gel. The Ala/Ala genotype generates two fragments of 89 and 18 bp. The heterozygote displays three fragments (107. 89 and 18 bp).

Statistical Analyses

Data for quantitative variables were expressed as median (minimum-maximum). Differences for the frequencies of the MnSOD polymorphisms between acromegaly patients and the control group were analyzed using the Chi-square test. The Hardy-Weinberg equilibrium was applied for all polymorphisms. While Student's *t*-test and Mann Whitney U were used to compare continuous data between two groups, one-way ANOVA and Kruskal-Wallis test were applied to compare continuous data between more than two groups. Bonferroni and Dunn's test were performed to adjust for multiple comparisons. Multiple linear regression analysis was applied for independent variables (age, gender, patient and healthy groups, plasma glucose, cholesterols, body mass index) on TAC and SOD levels as dependent variables. Spearman's coefficient was used to test for bivariate correlations. The threshold for significance was $p < 0.05$. The SPSS version 20.0 for Windows was used to perform statistical analysis (SPSS Inc. Chicago, IL, USA).

Results

Patient Characteristics

At the time of diagnosis, 7 (16.3%) patients had microadenomas and 36 (83.7%) patients had macroadenomas in acromegaly group. Tumor size of eight patients at the time of diagnosis was not available. The median disease duration was 4 (0.5–27) years in acromegaly patients. 28 (54.9%) patients and 9 (17.6%) patients were operated once and two times, respectively. Among 14 (27.5%) patients not operated, 4 patients were being followed with the first-line medical treatment and 10 patients were in the preoperative preparation. Disease activity was controlled in 24 patients and uncontrolled in 27 patients (naïve patients included). Seventeen patients in activity controlled and 13 patients in uncontrolled group were receiving somatostatin analogues.

Table 1 shows the characteristics of acromegaly patients and age-sex matched healthy controls. The median GH, IGF1 and IGF1 normalized were 1.5 (0.03–40) ng/mL, 376 (41–1,220) ng/mL and 132.4% (13–653) in the acromegaly patients, respectively. Body mass index (BMI), glucose and triglyceride levels were significantly elevated in acromegaly group ($p < 0.001$, $p = 0.001$ and $p = 0.002$ respectively). HDL levels were significantly decreased in the acromegaly patients ($p < 0.05$). 13 (25.5%) acromegaly patients and 12 (21.1%) healthy subjects were hypertensive ($p > 0.05$).

In comparisons according to disease activity (Table 2), controlled and uncontrolled acromegaly patients had higher BMI compared to healthy subjects ($p < 0.001$, $p = 0.006$ respectively). Also, glucose levels for uncontrolled patients and triglyceride levels for controlled patients were significantly elevated than those in the healthy subjects ($p = 0.001$ and $p = 0.001$ respectively). HDL levels were significantly decreased in controlled patients compared to healthy subjects ($p < 0.05$).

SOD Levels

The median SOD levels of the acromegaly patients and healthy subjects were 42.7 (33–60) U/mL and 46.3 (38–95) U/mL, respectively (Table 1). This difference was significantly lower in acromegaly patients ($p < 0.001$). Also there was a significant difference in SOD levels according to disease activity ($p = 0.001$). SOD levels were 43.1 (33–60) U/mL in controlled patients, 42.3 (34–55) U/mL in uncontrolled patients (Table 2). The difference was nearly significant between controlled patients versus healthy subjects ($p = 0.05$) and significant between uncontrolled patients versus healthy subjects ($p = 0.002$). However, there was no difference between controlled and uncontrolled acromegaly patients. Also SOD levels were not statistically different in patients receiving somatostatin analogues compared to patients not receiving ($p > 0.05$) (Data not shown).

SOD levels were analyzed according to MnSOD gene variants. The median SOD levels were found 43.6 (35–55) U/mL in VV genotype, 43.0 (33–60) U/mL in VA genotype and 41.2 (39–46) U/mL in AA genotype in

Table 1 Demographic Characteristics of Acromegaly Patients and Control Group

	Acromegaly (n = 51)	Control (n = 57)	p
Gender (Female/Male)	33/18	44/13	N.S.
Age (years)	44 (22–83)	42 (18–74)	N.S.
IGF1 (ng/mL)	376 (41–1,220)		
IGF1 norm (%)	132.4 (13–653)		
GH (ng/mL)	1.5 (0.03–40)		
SOD (pg/mL)	42.7 (33–60)	46.3 (38–95)	<0.001†
TAC (μM)	1,313.7 (155–1,902)	1,607.3 (195–1,981)	<0.001†
BMI (kg/m^2)	28 (19–36)	24 (19–32)	<0.001†
Hypertension (n, %)	13 (25.5)	12 (21)	N.S.
Glucose (mg/dL)	100 (74–392)	92.3 (74–119)	0.001†
Total Cholesterol (mg/dL)	187.5 (123–326)	192.5 (149–254)	N.S.
LDL (mg/dL)	124 (68–226)	125 (91–156)	N.S.
HDL (mg/dL)	45 (17–75)	49 (30–76)	<0.05*
Triglyceride (mg/dL)	119.5 (34–477)	86 (59–169)	0.002†

Data shown as median (minimum-maximum).
The Student's *t*-test * and Mann–Whitney U test † were applied.
BMI: Body Mass Index

patient group ($p > 0.05$). In healthy subjects, the median SOD level was 45.8 (38–80) U/mL in VV genotype, 47 (38–95) U/mL in VA genotype and 46.0 (38–65) U/mL in AA genotype group ($p > 0.05$).

Multiple regression analysis showed that acromegaly significantly decreased the SOD levels regardless of independent factors including age, gender, BMI, plasma glucose and cholesterols ($p < 0.001$). No correlation was found between SOD levels and these variables.

TAC levels

The median TAC levels of acromegaly patients and healthy subjects were 1,313.7 (155–1,902) μM and 1,607.3 (195–1,981) μM (Table 1). This difference was significantly lower in the acromegaly group ($p < 0.001$). Comparison of TAC levels according to the disease activity was also significant between controlled, uncontrolled and healthy groups ($p < 0.001$) (Table 2). Besides, no significant difference was found for TAC levels between controlled and uncontrolled acromegaly groups, TAC levels of uncontrolled patients were the lowest among three groups. Significantly decreased levels of TAC were found in controlled and uncontrolled acromegaly patients compared to the healthy subjects ($p < 0.05$, $p < 0.001$ respectively). Patients receiving somatostatin analogues displayed no statistical difference in TAC levels compared to patients not receiving ($p > 0.05$) (Data not shown).

TAC levels were inversely correlated with fasting glucose ($p = 0.005$, $r = –0.27$ respectively). Also a weak inverse correlation was found between TAC levels and BMI ($p = 0.007$, $r = –0.27$ respectively). Multiple regression analyses showed that acromegaly significantly decreased the TAC levels regardless of independent factors mentioned above ($p < 0.001$).

MnSOD polymorphism

Genotype distributions for MnSOD polymorphisms in patient and control groups were in agreement with Hardy Weinberg equilibrium ($p = 0.926$ for patients and $p = 0.356$ for healthy subjects). Genotypes and allele frequencies for MnSOD genotypes in acromegaly patients are given in Table 3. No difference was observed between acromegaly patients and healthy controls according to MnSOD genotypes. Table 4 summarizes the characteristics of acromegaly patients according to SOD genotypes. No association was observed between MnSOD genotypes, SOD and TAC levels. The difference in the total cholesterol levels were significant in acromegaly patients according to MnSOD genotypes ($p < 0.05$)

Table 2 Comparison of Acromegaly Patients According to Disease Activity

	Controlled (n = 24)	Uncontrolled (n = 27)	Healthy Subjects (n = 57)	p
Age (years)	43 (22–83)	46 (24–69)	42 (18–74)	N.S.
Gender (female/male)	17/7	16/11	44/13	N.S.
IGF1 (ng/mL)	172 (41–323)	590 (282–1,220)		N.A.
IGF1 norm (%)	75 (13–138)	224 (115–652)		N.A.
GH (ng/mL)	0.7 (0.03–2.1)	2.7 (0.6–40)		N.A.
SOD (U/mL)	43.1 (33–60)[a]	42.3 (34–55)[b]	46.3 (38–95)	0.001
TAC (μM)	1,358 (737–1,903)[c]	1,239 (155–1,817)[d]	1,607.3 (195–1,981)	<0.001
BMI (kg/m^2)	28.5 (21–36)[e]	28 (19–36)[f]	24 (19–32)	<0.001
Hypertension (n, %)	5 (20.8)	8 (29.6)	12 (21)	N.S.
Glucose (mg/dL)	95 (74–136)	108 (79–392)[g]	92.3 (74–119)	0.001
Total Cholesterol (mg/dL)	202 (123–293)	181 (131–326)	192.5 (149–254)	N.S.
LDL (mg/dL)	136 (69–184)	116 (68–226)	125 (91–156)	N.S.
HDL (mg/dL)	42 (19–75)[h]	46 (17–66)	49 (30–76)	<0.05
Triglyceride (mg/dL)	179 (34–414)[i]	100 (39–477)	86 (59–169)	0.001

Data shown as median (minimum-maximum)
Bonferroni correction for HDL and Dunn's test for the other variables were applied in posthoc analysis.
[a] $p = 0.05$ *vs.* Healthy, [b] $p = 0.002$ *vs.* Healthy
[c] $p < 0.05$ *vs.* Healthy, [d] $p < 0.001$ *vs.* Healthy
[e] $p < 0.001$ *vs.* Healthy, [f] $p = 0.006$ *vs.* Healthy
[g] $p = 0.001$ *vs.* Healthy
[h] $p < 0.05$ *vs.* Healthy
[i] $p = 0.001$ *vs.* Healthy

Table 3 Genotypes and Allele Frequencies for MnSOD Genotypes in Acromegaly

Genotype	Patients n (%)	Controls n (%)
VV	19 (37.3)	18 (31.6)
VA	24 (47.1)	31 (54.4)
AA	8 (15.7)	8 (14.0)

p value > 0.05

	Alleles	
V	62 (60.8)	67 (58.8)
A	40 (39.2)	47 (41.2)

p value > 0.05

and total cholesterol level was found significantly higher in VV patients compared to the carriers of VA genotype ($p < 0.05$). No other association was found between MnSOD genotypes and characteristics of acromegaly such as GH, GF1, IGF1 normalized and remission status.

Discussion

In the present study our aim was to investigate the effect of acromegaly on SOD and TAC levels, to reveal the associations regarding the disease activity and the possible influence of MnSOD polymorphism.

There are very limited studies investigating oxidative stress in acromegaly. Boero *et al.* revealed that acromegaly could increase oxidative stress through increasing oxidized low density lipoprotein and activity of ceruloplasmin, despite the fact that they observed no significant difference in the ceruloplasmin levels, myeloperoxidase activity and TBARS as an index of lipid peroxidation [7]. In that study, no significant difference was found in the total antioxidant capacity between active acromegaly patients and controls, although TAC levels were decreased in acromegaly patients. Previous studies also showed significantly decreased levels of catalase, increased levels of TBARS and also higher SOD activity in acromegaly patients, albeit insignificant [6]. Our study revealed the reduced antioxidative capacity in

Table 4 Characteristics of Acromegaly Patients According to SOD Genotypes

	VV	VA	AA
GH (ng/mL)	1.3 (0.03–40)	1.5 (0.3–17)	0.8 (0.03–8)
IGF1 (ng/mL)	303 (41–1,116)	465 (110–1,220)	197.5 (153–830)
IGF1 norm (%)	112 (13–653)	183 (41–457)	100 (57–424)
Remission (*n*, %)			
Controlled	11 (45.8)	8 (33.3)	5 (20.8)
Uncontrolled	8 (29.6)	16 (59.3)	3 (11.1)
SOD Level (U/mL)	43.5 (35–55)	42.9 (33–60)	41.2 (39–48)
TAC (μM)	1,313.7 (735–1,179)	1,326.3 (155–1,817)	1,204.8 (484–1,903)
Glucose (mg/dL)	97 (74–127)	108 (79–392)	96 (86–284)
Total Cholesterol (mg/dL)	221 (123–326)[a]	180 (142–249)	180 (131–247)
LDL (mg/dL)	146.5 (69–226)	120 (78–160)	116 (68–160)
HDL (mg/dL)	42.5 (17–75)	46 (26–61)	45 (35–56)
Triglyceride (mg/dL)	134 (70–477)	103 (34–271)	154 (85–216)
BMI (kg/m^2)	28 (20–35)	29 (19–37)	27 (22–31)

Data shown as median (minimum-maximum)
[a] $p < 0.05$ *vs.* VA (Bonferroni correction)

acromegaly patients through significantly decreased levels of SOD and TAC compared to the healthy controls. Our study is distinguished from the other studies with respect to sample size (as both of the previous studies included 15 acromegaly patients) and measurement procedure of TAC levels. It has been established in the literature that not all antioxidant assays respond equally well to serum antioxidants, and in the present study, total antioxidant capacity was measured by the CUPRAC method which has some distinct advantages over other similar assays in regard to its realistic pH, accessibility and stability of reagents, responsiveness to thiol antioxidants, favorable redox potential and applicability to both lipophilic and hydrophilic antioxidants [20]. Our findings suggested that the decreased levels of SOD and TAC could have an unfavorable effect on oxidative stress in acromegaly patients.

The improvement of endothelial dysfunction after disease control in acromegaly has been demonstrated in several studies, as well as the strong association between active acromegaly and endothelial dysfunction. These studies demonstrated that flow-mediated dilatation and endothelial cell markers were significantly lower in uncontrolled and also controlled acromegaly patients than healthy subjects [2, 21]. In another study, it was also shown that impaired carotid intima-media thickness and brachial-ankle pulse wave velocity could persist after transsphenoidal surgery [22]. Present study showed that although the levels of SOD and TAC were higher in controlled acromegaly patients than those with uncontrolled disease activity, uncontrolled and also controlled acromegaly patients had the decreased levels of SOD and TAC compared to healthy subjects. Along with the association between oxidative status and endothelial dysfunction, our findings suggested that the decreased SOD and TAC levels in controlled and uncontrolled acromegaly might be one of the key mechanisms of the endothelial dysfunction. The parameters of endothelial dysfunction such as flow-mediated dilatation and endothelial cell markers were not assessed in the present study and this might be considered as a limitation. Further studies focused on this association are needed.

In the present study, potential confounders including use of somatostatin analogues, BMI and metabolic parameters should be considered. In the literature, there were limited studies of acromegaly that focused on the effect of somatostatin analogues on oxidative stress. This study displayed no difference in patients receiving somatostatin analogues compared to patients not receiving. Yarman *et al.* revealed that naïve acromegaly had increased TBARS levels and after short acting octreotide administration, plasma levels of TBARS decreased sig-

nificantly during 24 h follow up in 12 acromegaly patients [23]. However, the TBARS test may not be a selective marker of oxidative stress, and is known to be responsive to interfering substances other than the secondary products of lipid peroxidation [24]. Several previous reports revealed that the decreased levels of SOD and TAC could be attributed to metabolic conditions such as diabetes, obesity and hyperlipidemia [12, 25, 26]. On the other hand, in a study focused on the influence of metabolic parameters on oxidative stress, SOD levels were not different in groups stratified by the number of components of metabolic syndrome and no correlation was found between SOD levels and metabolic parameters such as BMI, fasting glucose, triglycerides and HDL [27]. In agreement with Abdilla *et al.*, no correlation was observed between SOD levels and metabolic parameters in the present study. Multiple regression analysis also showed that the effect of acromegaly still remained on SOD and TAC levels independent of the metabolic parameters effect.

Another aim of this study was to investigate the possible associations between MnSOD polymorphism and acromegaly. MnSOD polymorphism regulates the import of human manganese superoxide dismutase into the liver mitochondria [28]. The MnSOD exon 2 polymorphism (rs 4880) leads to a valine to alanine substitution which results in a structural alteration from a β sheet to an α helix, causing a 30–40% increase in mitochondrial MnSOD activity (4). The MnSOD Val16Ala polymorphism has been attributed to the increased risk of oxidative stress associated with pathological conditions such as coronary artery disease, hypercholesterolemia, type 2 diabetes and diabetic complications [17, 18, 29, 30]. MnSOD polymorphism varies in different populations with higher Ala allele frequencies (41–62%) reported in Caucasians than the 11–30% in Asians [31-34]. Our study was consistent with the previous findings in Turkish population as Ala allele frequency occurred in 41.8% of controls and 38.9% of patients with acromegaly [35, 36]. No significant difference in MnSOD polymorphism was found between acromegaly patients and controls. Our findings also revealed that the increased levels of SOD were not associated with MnSOD polymorphisms in acromegaly. In the present study, there was no significant difference in the level of SOD according to the genotypes in control group. This insignificancy could be explained by the limited number of subject in AA genotype of control group. Additionally, similar to our study there are several reports such as the study of Becer *et al.* reported no difference in SOD levels between MnSOD genotypes in healthy subjects [37]. It was demonstrated that MnSOD binding protein could modulate the SOD levels at the stage of post transcriptional regulations [38]. Possible epigenetic alterations including methylation and acetylation may also play an important role in the regulation of the SOD levels regardless of MnSOD polymorphism [39]. However further studies are needed to clarify the pathological mechanisms involved in the alterations of SOD levels.

In conclusion, this study showed that acromegaly was associated with decreased levels of SOD and TAC which could be one of the key mechanisms in endothelial dysfunction. Moreover, controlling the disease activity could not adequately improve these levels. With respect to explaining genetic alterations, MnSOD polymorphism did not have an influence on these levels and disease characteristics. Further studies are needed to support the impact of controlling disease activity on oxidative stress and to better understand the underlying mechanisms involved.

Conflict of Interest

The authors declare no conflict of interest.

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